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BIRCH STEWART KOLASCH & BIRCH			JUEDES, AMY E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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mailroom@bskb.com

Office Action Summary	Application No. 10/509,055	Applicant(s) SAGAWA ET AL.
	Examiner AMY E. JUEDES	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 16 August 2010.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-3,5-8,10,12,14-29,31-35 and 37-39 is/are pending in the application.

4a) Of the above claim(s) 8 and 14-27 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-3,5-7,10,12,28,29,31-35 and 37-39 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsman's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date 8/16/10

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____

5) Notice of Informal Patent Application

6) Other: _____

DETAILED ACTION

1. Applicant's amendment and remarks, filed 8/16/10, are acknowledged.
Claims 1 and 28-29 have been amended.
Claims 1-3, 5-8, 10, 12, 14-29, 31-35, and 37-39 are pending.
2. Claims 8 and 14-27 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-3, 5-7, 10, 12, 28-29, 31-35, and 37-39 are being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
Claims 1-3, 5-7, 10, 12, 28-29, 31-35, and 37-39 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for expanding cytotoxic lymphocytes, a method for increasing expression of IL-2 receptor in cytotoxic lymphocytes, and a method for increasing the number of CD8 positive cells comprising culturing peripheral blood mononuclear cells in the presence of at least one recombinant fibronectin fragment together with IL-2, does not reasonably provide enablement for:

A method for expanding cytotoxic lymphocytes, a method for increasing expression of IL-2 receptor in cytotoxic lymphocytes, and a method for increasing the number of CD8 positive cells comprising culturing umbilical cord blood mononuclear cells in the presence of at least one recombinant fibronectin fragment together with IL-2.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the

inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)* The MPEP further states that physiological activity can be considered inherently unpredictable.

The instant claims are drawn to methods of expanding cytolytic lymphocytes, increasing IL-2R and increasing the number of CD8 positive cells in cytotoxic lymphocytes comprising culturing precursor cells capable of differentiating into cytotoxic lymphocytes with IL-2 and fibronectin, such that the resulting cytotoxic lymphocytes maintain cytotoxic activity longer than cytotoxic lymphocytes cultured in the absence of fibronectin. The claims recite that the precursor cells include peripheral blood mononuclear cells, NK cells, umbilical cord blood mononuclear cells, and hematopoietic stem cells, or blood components containing these cells. Peripheral blood mononuclear cells are known to be a suitable precursor population for the differentiation of cytotoxic lymphocytes, including CTL and LAK cells (see Jung et al.). However, the use of other precursor cells for differentiation into a cytolytic lymphocyte population with fibronectin and IL-2 is unpredictable. For example, umbilical cord blood lymphocytes are different in phenotype and function from lymphocytes of normal adults, with cord blood lymphocytes displaying a functionally immature phenotype (see Lucivero et al., page 260, in particular). In fact, stimulants such as anti-CD3 fail to induce proliferation of cord blood lymphocytes (see page 260, in particular). Thus, differentiation of cord blood lymphocytes into a population of cells comprising enhanced cytolytic activity would be highly unpredictable. Additionally, hematopoietic stem cells are even more immature than umbilical cord blood cells, and attempts to obtain mature T cells by culture with IL-2 using CD34+ hematopoietic stem cells have been without notable success (see Pawelec et al., 1998). Furthermore, while fibronectin enhances the cytotoxicity of cytotoxic T lymphocytes, it does not enhance natural killer cell activity (see Katzman et al., 1987 and Ybarrondo et al, of record). Thus, using fibronectin to induce longer cytotoxic activity in NK cells would be highly unpredictable.

Thus, based on the unpredictability of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims. The specification demonstrates that peripheral blood mononuclear cells cultured with fibronectin display enhanced cytolytic activity, CD8 and IL-2R expression. However, no examples or guidance are provided for differentiating other precursor cells, including NK cells, hematopoietic stem cells, or umbilical cord blood cells to cytolytic lymphocytes. Therefore, based on the unpredictability of the art and the lack of guidance provided by the instant specification, it would require undue experimentation to practice the invention as broadly claimed.

Applicant's arguments filed 8/16/10 have been fully considered, but they are not persuasive.

Applicant argues that based on the publication by Nelson et al., the ordinary

artisan would have readily understood that cytotoxic lymphocytes could have been obtained using peripheral blood mononuclear cells or umbilical cord blood mononuclear cells.

Nelson et al. teach that cord blood cells stimulated with anti-CD3 upregulate IL-2R. Lucivero et al., cited above, also indicate that cord blood cells stimulated with anti-CD3 upregulate IL-2R. However, the instant claims are drawn to a method of expanding/differentiating cytotoxic lymphocytes from a precursor cell. Both Nelson et al. and Lucivero et al. teach that cord blood T cells differ functionally from adult peripheral blood T cells. For example, Nelson et al. teach that cord blood T cells fail to produce soluble IL-2R in response to anti-CD3 stimulation, which indicates that the T cells might not be fully functional (see page 138, in particular). Furthermore, as noted above, Laciverto et al. teach that cord blood T cells fail to proliferate in response to anti-CD3. Thus, the state of the art is such that cord blood T cells appear to be not fully functional compared to adult peripheral blood T cells. Thus, differentiating T cells capable of mediating cytotoxic activity from cord blood precursor cells would be highly unpredictable. Applicant has not cited any evidence demonstrating that differentiating cytotoxic T cells from cord blood precursor cells is routinely performed in the art, as is the case for adult peripheral blood cells.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-3, 5-7, 10, 12, 28-29, 33-35, and 37-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Jung et al., 1987, in view of Cardarelli et al., 1991 (of record), U.S. Patent 5,198,423 (of record), Ybarrondo et al., 1997 (of record), and Neri et al., 2001 (or record).

As set forth previously, Jung et al. teach a method of differentiating cytotoxic CD8+ T lymphocytes comprising culturing PBMCs with anti-CD3 (see page 3718-3719, in particular). Jung et al. teach evaluating cytotoxicity using a radioactively labeled target cell (see page 640, in particular). Jung et al. teach that culturing for 2-3 days results in the greatest CTL activity (see page 641 in particular), which also corresponds to the peak in proliferation and IL-2 receptor expression by the lymphocytes (see Fig. 1-2, in particular). Jung et al. teach that by 4 days in culture, cytotoxicity, proliferation, and IL-2 receptor expression begin to decline.

Jung et al. do not teach incubating the cells with a recombinant fibronectin fragment comprising SEQ ID NO: 12, IL-2, nor evaluating cytotoxicity using calcein-AM labeled target cells.

Cardarelli et al. teach that the addition of immobilized fibronectin and IL-2 to PBMC cultures stimulated with anti-CD3 enhances proliferation and IL-2R expression of T lymphocytes. In particular, Cardarelli et al. teach that the combination of fibronectin, IL-2, and anti-CD3 induces high level of proliferation after 4 days in culture (see Fig. 1, in particular). Cardarelli et al. further teach that the regions of fibronectin responsible for its activity on T cells are the RGD cell binding domain and the EILDV amino acid sequence (see page 115, in particular). Cardarelli et al. also teach that the cells can be cultured at a concentration of 10^5 cells/well of a microtiter plate (i.e. at a concentration between 1 and 5×10^5 cells/ml). Ybarrondo et al. teach that immobilized fibronectin provides a costimulatory signal to CTL, that induces an enhanced degranulation response after TCR crosslinking. Ybarrondo et al. teach that degranulation is a mechanism by which CTL lyse target cells.

The '423 patent teaches a biologically active recombinant fibronectin fragment comprising SEQ ID NO: 12 (see columns 3-4 in particular). Said fragment comprises the RGD and EILDV sequences (see columns 3-4 in particular). The '423 patent also teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses (see column 1 in particular).

Neri et al. teach a method of evaluating CTL activity by labeling target cells with calcein-AM, and detecting fluorescence released by lysed target cells (i.e. determining fluorescent intensity ascribed to destroyed target cells, see page 1131, in particular). Neri et al. teach that the method is convenient, rapid, and sensitive, and avoids the problems associated with handling and disposal of radioactive materials (see page 1131, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include immobilized fibronectin and IL-2, as taught by Cardarelli et al. and Ybarrondo et al., in the method of differentiating CTL taught by Jung et al. The ordinary artisan would have been motivated to do so, since Cardarelli et al. teach that fibronectin and IL-2 enhance the expansion of T cells cultivated under conditions identical

to those of Jung et al. Additionally, the ordinary artisan would have a reasonable expectation of success in obtaining cytolytic cells that maintain cytotoxicity past 3 days in culture (i.e. longer cytotoxicity), since Cardarelli et al. teach that the inclusion of fibronectin and IL-2 results in sustained high levels of proliferation after 4 days in culture, and Jung et al. teach that high levels of proliferation and IL-2 receptor expression correlate with high levels of cytotoxicity. Additionally, Ybarrondo et al. teach that fibronectin acts as a costimulatory molecule for CTL, resulting in an enhanced degranulation response (i.e. enhanced or "longer" cytotoxicity towards a target cells). Furthermore, the ordinary artisan would have been motivated to substitute the recombinant fibronectin fragment taught by the '423 patent, for the purified human fibronectin in the method of Ybarrondo et al. or Cardarelli et al., since the '423 patent teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the recombinant fibronectin fragment, since the '423 patent teaches that the recombinant fibronectin is a biologically active fragment, and it comprises the sequences taught by Cardarelli et al. as being important for T cell stimulation. Furthermore, it would have been obvious to replace the radioactive cytotoxicity assay of Jung et al., with the calcein-AM cytotoxicity assay taught by Neri et al. The ordinary artisan would have been motivated to do so, since Neri et al. teach that the calcein-AM assay is convenient, rapid, and sensitive, and avoids the problems associated with handling and disposal of radioactive materials. Additionally, it would have been obvious to culture the cells in a petri dish, a flask, or a bag, since these are all well known and routine vessels used for performing tissue culture.

Applicant's arguments filed 8/16/10 have been fully considered, but they are not persuasive.

Applicant argues that Jung et al. teach that cytotoxicity correlates with RNA rather than DNA synthesis. Thus, Applicant concludes that theh ordinary artisan could not have been reasonably certain that fibronectin, which Cardarelli teaches increases cell proliferation, could also have affected the induction and maintenance of cytotoxicity.

Jung et al. teach that induction of proliferation lags behind induction of cytotoxicity, as noted by Applicant. However, Jung et al. also teach that the decline of cytotoxicity, proliferation, and IL-2R expression follow identical kinetics, with a peak at 2-3 days, and a decline thereafter. As noted above, Cardarelli et al. teach that the fibronectin extends the proliferation of T cells to more than 4 days of culture. The ordinary artisan would have expected that factors which increase the survival and expansion of T cells in culture would likewise result in sustained and prolonged T cell activities in the resulting T cells (such as cytotoxic activity). Furthermore, Cardarelli et al. teach that fibronectin enhances IL-2R expression. Thus, the ordinary artisan would be motivated to include fibronectin to increase the proliferative lifespan and IL-2R

expression of the T cells in culture, and the ordinary artisan would have reasonable expectation that this would result in the prolonged maintenance of other T cell activities that correlate with proliferation, such as cytotoxicity. Furthermore, as noted above, Ybarrondo et al. teach that immobilized fibronectin provides a costimulatory signal to CTL, that induces an enhanced degranulation response after TCR crosslinking. Thus, the ordinary artisan would have been motivated to include fibronectin to enhance CTL activity. Thus, based on the combination of references, the ordinary artisan would have been motivated to include fibronectin to enhance T cell expansion and cytolytic activity (i.e. maintain longer cytotoxicity activity).

2. Claims 31-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Jung et al., 1987, Cardarelli et al., 1991, U.S. Patent 5,198,423, Ybarrondo et al., 1997, and Neri et al., 2001, as applied to claims 1-7, 10, 12, 28-29, 33-35, and 37-39 above, and further in view of Chen et al., 1994 (of record).

As set forth previously, The combined teachings of Jung et al., Cardarelli et al., U.S. Patent 5,198,423, Ybarrondo et al., and Neri et al are described above.

They do not teach transducing a foreign gene into the T cells.

Chen et al. teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro with maintenance of function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells (see pages 3634-3635, in particular).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to further transduce the cytotoxic T lymphocytes made by the method of Jung et al., Cardarelli et al., U.S. Patent 5,198,423, Ybarrondo et al., and Neri et al, with a retrovirus encoding PKC, as taught by Chen et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, and have a reasonable expectation of success, since Chen et al. teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro with maintenance of function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells.

Applicant argues that the instant claims are not obvious for the same reasons set forth above.

The instant claims stand rejected for the reasons set forth above.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-3, 5-7, 10, 12, 28-29, 31-35, and 37-39 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 20-21 of copending Application No. 10/568,745, in view of Jung et al. and Neri et al., 2001.

As set forth previously, The '745 application claims a method for preparing a cytotoxic lymphocyte comprising the step of inducing the cytotoxic lymphocyte from a precursor cell by culturing the precursor cell in the presence of a fibronectin or a fragment thereof. The '745 application further claims that the fibronectin fragment comprises SEQ ID NO: 13, which is the same as SEQ ID NO: 12 of the instant application. The '745 application also claims that the fibronectin is immobilized on a substrate and that the concentration of cells is between 1 cell/ml to 5 x 10⁵ cells per ml. The '745 application also claims that the lymphocytes can be transfected with a foreign gene using a retrovirus, adenovirus, or simian virus. Additionally, it would be obvious to us PBMC as the precursor cells, since Jung et al. teach that PBMC can be induced to develop into cytotoxic T cells. Additionally, Jung et al. teach that both IL-2 and anti-CD3 can be used to enhance the development of different types of cytotoxic lymphocytes from PBMC

precursors. Therefore, it would have been obvious to include IL-2 and/or anti-CD3 to enhance cytolytic lymphocyte differentiation. Furthermore, it would have been obvious to evaluate cytolytic activity with a method comprising determining lysis of target cells labeled with calcien-AM as taught by Neri et al,

This is a provisional obviousness-type double patenting rejection.

Applicant argues that the instant application has an earlier filing date than the '745 application, and that the double patenting rejection should be withdrawn in the early filed application if it is the only rejection remaining.

However, the obviousness type double patenting rejection is maintained, since the instant claims are rejected on other grounds.

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 8am to 4:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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